6. A CDR or functional fragment thereof, comprising substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, wherein said CDR or functional fragment thereof specifically binds a neoplastic cell or antigen thereof.

REMARKS

Claims 1-48 are pending in the above-identified application. Claims 1-6, 47 and 48 are currently under examination.

By the present communication claims 1 and 6 have been amended. Support for the amendments to the claims can be found in the specification including, for example, on page 5, lines 22-26; page 13, line 32, through page 14, line 8; page 15, lines 19-31; and page 34, lines 16-28. Accordingly, the amendments do not introduce new matter. Furthermore, Applicants respectfully submit that entry of the amendments after final is proper because the amendments place the claims into condition for allowance or in better form for consideration on appeal, and do not raise new issues for consideration in accordance with 37 CFR 1.116 and MPEP 714.12 and 714.13. Therefore, entry of the amendments is respectfully requested. A marked-up copy of the claims showing the amendments is attached hereto as Appendix A.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-6, 47 and 48 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not reasonably provide enablement for a human monoclonal antibody which does not contain a full set of six CDRs or a functional fragment thereof or a CDR alone. The Office Action alleges that the art cited in the response mailed February 20, 2001, is not commensurate in scope with the enablement provided in the specification.

Applicants respectfully traverse the rejection and maintain that the full scope of the claimed invention is enabled because functional fragments of antibodies were known in the art and the specification provides guidance commensurate with that which was known in the art to allow one skilled in the art to make and use the claimed functional fragments. Applicants further maintain that the references provided as Exhibits in the response mailed February 20, 2001, exemplify the level of skill in the art with regard to the scope of enablement provided in the specification for the reasons set forth below.

Applicants respectfully disagree with the assertion in the Office Action that Ward et al. teach that the VH domains are "sticky" and it is not clear if affinity of the VH domains is influenced by the stickiness. Although Ward et al. describes some VH fragments as being "sticky" on page 546, column 1, lines 16-18, Ward et al. also describes a number of VH fragments that have specificity that is not due to mere "stickiness," as set

forth below. Because the claims require that the claimed antibody or functional fragment thereof specifically binds a neoplastic cell or antigen thereof, any VH domain that is merely sticky without having specificity is not encompassed by the claims.

As referred above, Ward et al. describes a number of VH domains that have binding specificity. For example, Ward et al. describes on page 545, column 1, lines 23-25 that

> The VH domains were purified and affinities for lysozyme determined (Table I). The affinities, in the 20 nM range, are similar to those of the VH domain of the D1.3 antibody.

Applicants respectfully submit that affinity in the 20 nM range is not mere "stickiness." Rather affinity in the 20 nM range is indicative of specific affinity. The assertion that 20 nM affinity is not mere "stickiness" is supported by the description in Ward et al. on page 546, column 1, lines 7-10, where it is stated that

> [t]he affinity of the VH domains (20 nM or $5x10^7$ M^{-1}) for lysozyme lies within the range expected for the affinities of monoclonal antibodies for protein antigens, and can be improved by site directed mutagenesis.

Further in regard to the binding specificity of the VH fragments, Ward et al. states on page 545, column 1, lines 24-29 that

> To check the specificity of binding, the three VH domains were also screened for binding to four other purified proteins (bovine serum albumin, insulin, keyhole-limpet haemocyanin (KLH) and cytochrome c), and to foetal calf serum, milk powder and plastic micrototer plates. No binding was detected.

Thus, it is clear from Ward et al. that the affinity of the VH fragments for substrate is due not to non-specific stickiness but to specific binding affinity.

Furthermore, Applicant disagrees with the assertion in the Office Action that Ward et al. only describes a VH produced using a diverse library of VH genes and screened for binding. Rather, Ward et al. describes cloning of the VH domain from the D1.3 antibody, and subsequent expression and binding analysis of this VH-D1.3 fragment (see the legend to Figure 1 on page 545). In regard to the other VH fragments that were produced by screening a diverse library of VH genes, fragments produced by such methods are encompassed in the scope of the claims because the claims are composition claims and are not limited to any process for producing the recited monoclonal antibody, or functional fragment thereof. Moreover, the specification teaches methods for making and screening diverse libraries of antibodies, or functional fragments thereof (see, for example, page 26, lines 11, through page 27, line 25). Thus, the enablement provided in the specification with regard to the claimed CDRs is commensurate in scope with that which was known in the art as demonstrated by the description in Ward et al. of antibody fragments that were able to specifically bind a substrate.

Applicants respectfully disagree with the assertion in the Office Action that Williams et al. describes a dimeric peptide as being required for binding. Rather, Williams et al. describes a monomeric VL fragment as having binding affinity. Specifically, Williams et al. states on page 5538, column 2, lines 2-9 that

> Without Con A, V_LSH peptide (which is dimeric and can cross-link the receptor) markedly inhibited spontaneous lymphocyte proliferation, whereas the V_L peptide (which is monomeric and cannot cross-link the receptors) had no significant effect. However, in the presence of Con A (which should aggregate the receptors), both V_LSH peptide and V_L peptide had similar effects in inhibiting lymphocyte proliferation.

Although Williams et al. describes dimerization of the receptor as being required to inhibit spontaneous lymphocyte proliferation, Williams et al. does not describe dimerization of the VL fragment as required for binding. Rather, the description in Williams et al. that the monomeric VL fragment was capable of inhibiting spontaneous lymphocyte proliferation when the receptor was aggregated by ConA indicates that the monomeric VL was indeed capable of binding to the receptor. Thus, the enablement provided in the specification with regard to the claimed CDRs is commensurate in scope with that which was known in the art as demonstrated by the description in Williams et al. of antibody fragments that were able to specifically bind a substrate.

Applicants maintain that Ditzel et al. provides evidence that the specification is enabling for the claimed antibody fragments including the CDR, or fragment thereof, of claim 6. Ditzel et al. describes a CDR domain having binding activity, the domain including the addition of two cysteines that allow cyclization of the peptide for improved affinity (see page 745, column 1, first full paragraph). This description is commensurate in scope with the teaching in the specification for modifying a functional antibody fragment to improve affinity. In this regard, the specification teaches on page 26, lines 1-5, that isolated nucleic acids encoding tumor-specific human monoclonal antibodies or functional fragments thereof can be engineered to produce antibodies with optimal properties such as affinity, selectivity, avidity, stability or bioavailability. The specification further teaches on page 26, lines 5-10, that such modifications can include, for example, addition, deletion, or substitution of amino acids. Thus, the enablement provided in the specification with regard to the claimed CDRs is commensurate in scope with that which was known in the art as demonstrated by the description in Ditzel et al. of CDR domains that were able to specifically bind a substrate.

Regarding the description of CDR shuffling by Ditzel et al., Applicants respectfully point out that this description was provided in the response mailed February 20, 2001, as evidence in regard to the enablement of the embodiments of the claimed invention wherein an antibody or functional fragment thereof has two or more CDRs. As set forth in the previous response, Ditzel et al. describes a number of antibody fragments produced by CDR

shuffling that retain binding activity for the antigens of the parent antibody on page 742, column 1, line 10, through column 2, line 15. Thus, the enablement provided in the specification for embodiments of the claimed composition wherein two or more CDRs are present in an antibody or functional fragment thereof in an altered order or context relative to a parent antibody is commensurate with that which was known in the art as demonstrated by Ditzel et al.

Similarly, Applicants provided Walsh in support of embodiments of the claimed invention where an antibody, or functional fragment thereof, contains one or more grafted CDR. Specifically, Walsh et al. describes in Table I a number of antibodies containing one or more grafted CDR and maintaining sufficient binding function to be used as diagnostic and therapeutic agents, the agents including ReoPro, Rituxan, Zenapax, Simulaect, Remicade, Synagis, Herceptin and Mabthera. Thus, the enablement provided in the specification for the claimed embodiments in which more than one CDR are grafted is commensurate with that which was known in the art as demonstrated by Walsh.

Regarding the assertion in the Office Action that the specification is not enabled for any VH or VL alone or a single CDR from any of SEQ ID NO:2 or 4 as claimed, Applicants respectfully point out that the claims require that the antibody or functional fragment thereof specifically binds a neoplastic cell or antigen thereof. Thus, any VH or VL that is not capable of specifically binding a neoplastic cell or antigen thereof is

not encompassed by the claims. As set forth above, Ditzel et al. by describing a number of antibody fragments, including VH, VL and CDR domains, having specific binding activity demonstrates that the enablement provided in the specification is commensurate with that which was known in the art. Accordingly, Applicants request withdrawl of the rejection of claims 1-6, 47 and 48 under 35 U.S.C. § 112, first paragraph.

Claim 5 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because there is insufficient guidance for using the claimed pharmaceutical compositions for the treatment of cancer. In this regard, the Office Action alleges that enablement of the claimed pharmaceutical composition is considered to rest on a teaching of in vivo administration for purposes of treating cancer.

Applicants respectfully traverse the rejection and submit that the rejection is not commensurate with the scope of the claimed subject matter. Claim 5 is a *composition* claim directed to a pharmaceutical composition, comprising the human monoclonal antibody or functional fragment of claim 1 and a pharmaceutical carrier. The claim does not recite and, therefore, is not limited to a *method* of in vivo administration for purposes of treating cancer.

> When a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that would reasonably correlate with the entire scope of that claim

> is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable *each* disclosed use. In other words, if *any* use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

MPEP § 2164.01(c), fourth paragraph, emphasis added. Applicant respectfully submits that the specification teaches multiple uses for the claimed pharmaceutical compositions including, for example, administration to reduce the proliferation or viability of neoplastic cells (see page 28, lines 15-17, and page 30, lines 8-12) or to detect neoplastic cells (see page 28, lines 12-18). Applicant maintains that the Office Action does not establish a proper case for nonenablement because the Office Action has not included an explanation, sufficiently supported by the evidence, why the specification fails to enable *each* disclosed use of the claimed pharmaceutical composition in accordance with MPEP § 2164.01(c).

Applicants maintain that the specification enables one skilled in the art to make and use the claimed pharmaceutical composition for the reasons set forth in the previous response. Further to the arguments of record, Applicants submit that the specification sufficiently enables one skilled in the art to use the claimed composition to detect neoplastic cells. The specification teaches detecting neoplastic cells by contacting a

sample with a human monoclonal antibody or functional fragment having substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, and detecting the specific binding of the human monoclonal antibody or functional fragment to the sample, wherein the presence or increased level compared to a normal cell of the human monoclonal antibody or functional fragment indicates the presence of or predisposition to cancer (see page 32, lines 12-21). The specification further provides working examples demonstrating the detection of neoplastic cells with the LH11238 antibodies which have substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4 as recited in the claims. For example, the specification demonstrates use of the LH11238 antibody for detection of breast carcinoma and ovarian carcinoma cells using an ELISA method (see Example II) and detection of H3464 breast carcinoma cells using a fluorescent activated cell sorting (FACS) based method (see Example III). Thus, the specification sufficiently enables one skilled in the art to make and use the claimed pharmaceutical composition. Accordingly, Applicants request withdrawl of the rejection of claim 5 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-6, 47 and 48 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting the term "substantially." In this regard, the Office Action alleges that the term substantially is a relative term and not clearly defined in the specification. The Office Action further alleges that it is not clear which of the well known methods of sequence

comparison would be used to determine a sequence that is substantially the same as the sequences recited in the claims. The Office Action further alleges that one skilled in the art would not know which of the definitions of CDR to use to determine the metes and bounds of the claim.

Applicants respectfully traverse the rejection. Applicants respectfully disagree with the assertion in the Office Action that the term "substantially" is not clearly defined in the specification. As set forth in the previous response, the term substantially is defined in the specification on page 8, lines 5-16, where the specification teaches that

> An amino acid sequence which is substantially the same as a heavy or light chain CDR exhibits a considerable amount or extent of sequence identity when compared to a reference sequence. Such identity is definitively known or recognizable as representing the amino acid sequence of the particular human monoclonal antibody. Substantially the same heavy and light chain CDR amino acid sequence can have, for example, minor modifications or conservative substitutions of amino acids. Such a human monoclonal antibody maintains its function of selectively binding a tumor-specific antigen.

The specification teaches that two CDRs can be compared by a structural comparison of their sequences. According to the teaching and guidance provided in the specification one skilled in the art would have been able to use the primary sequence structure recited in the claims as a reference sequence in any of a variety of known sequence comparison methods to compare to a

primary sequence structure of interest. One skilled in the art would have been able to identify a substantially similar sequence based on the results of such a structure comparison according to known criteria such as identity to the reference sequence or the presence of minor modifications or conservative substitutions compared to the reference sequence as taught in the specification.

Furthermore, as set forth above, the specification teaches that a substantially similar sequence would be identifiable according to having maintained a function of the reference sequence. The claims, as amended, recite that the antibody, or functional fragment thereof, specifically binds a neoplastic cell or antigen thereof. According to the teaching and guidance provided in the specification, one skilled in the art would have been able to further identify a substantially similar sequence by the function recited in the claims.

Regarding the alleged lack of clarity as to which of the well known methods of sequence comparison to use to determine a sequence that is substantially the same as the sequences recited in the claims, Applicants respectfully submit that one skilled in the art would have been able to use *any* method of sequence comparison capable of carrying out the comparison taught in the specification. A variety of sequence comparison methods are known and available in the art. Procedures and algorithms for such sequence comparison methods are accessible and their capabilities adequately known to those skilled in the art to allow them to evaluate wether or not a particular sequence

comparison method can perform the comparison described in the specification.

Regarding which of the definitions of a CDR to use in comparing a sequence to a CDR of SEQ ID NO:2 or 4, Applicants submit that in view of the teaching and guidance provided in the specification, one skilled in the art would have known that any of the CDR definitions can be used so long as the same CDR definition is used in any particular comparison. In this regard, the specification teaches on page 8, line 32, through page 9, line 1, application of *either* the Chothia, Kabat or MacCallum CDR definition to define a CDR. Furthermore, the specification teaches that the different CDR definitions include different positions in an antibody sequence and cover different lengths of sequence (see Table I on page 9). In view of the teaching provided in the specification, one skilled in the art would have understood that comparison of CDR sequences is performed using the same CDR definition for the reference and query sequence and not a different definition for each because application of different definitions would result in non-overlapping sets of residues in one or both of the sequences to be compared. Accordingly, one skilled in the art would have understood from the teaching in the specification that the same CDR definition is used for sequence comparison to identify substantially similar sequences. Therefore, Applicants request withdrawl of the rejection of claims 1-6, 47 and 48 under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

November 5, 2001
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Filed: December 2, 1998

APPENDIX A

Marked up versions of claims 1 and 6, showing amendments are provided below.

1. (Twice amended) A human monoclonal antibody or functional fragment thereof, comprising at least one Complementarity Determining Region (CDR) having substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, wherein said antibody or functional fragment thereof specifically binds a neoplastic cell or antigen thereof.

6. (Twice amended) A CDR or functional fragment thereof, comprising substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, wherein said CDR or functional fragment thereof specifically binds a neoplastic cell or antigen thereof.